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Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans; a systematic review

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ABSTRACT

Background: Transcutaneous Vagus Nerve stimulation (tVNS) may be an alternative to surgically implanted VNS for epilepsy and other diseases. However, its safety and tolerability profile is unclear.
Objective: We performed a systematic review of treatment harms from tVNS in humans.
Methods: A systematic published and grey literature search was carried out to identify studies which deployed tVNS in human subjects. Study authors were contacted for safety/tolerability data if these were not available in the publication. Databases were searched from 1966 to May 2017. We noted study type, population, stimulation parameters, type and prevalence of side effects and/or serious adverse events (SAE). We also noted whether side effects/SAE were considered to be related to the tVNS and the proportion of participants dropping out of studies due to side effects.
Results: 51 studies were included comprising a total of 1322 human subjects receiving tVNS. The most common side effects were: local skin irritation from electrode placement (240 participants, 18.2%), headache (47, 3.6%) and nasopharyngitis (23, 1.7%). Whilst heterogeneity in overall side effect event rates between studies was not accounted for by the frequency (Hz) or pulse width (ms) of stimulation, a minority (35 participants (2.6%)) dropped out of studies due to side effects. Overall, 30 SAE occurred but only 3 were assessed by the relevant researchers to be possibly caused by tVNS.
Conclusion: tVNS is safe and well tolerated at the doses tested in research studies to date.
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1. Introduction

The Food and Drug Administration (FDA) approved VNS as an adjunctive treatment for epilepsy in 1997 and for refractory depression in 2005. To date, >90,000 patients have been successfully implanted with VNS [1]. Owing to the multiple mechanisms of action, VNS has also been trialled as a potential treatment for other diseases such as rheumatoid arthritis [2], and heart failure [3].

Whilst traditionally, VNS has involved implantation of an electrical device alongside the left sided cervical branch of the vagus nerve in the chest wall, this requires a general anaesthetic with the attendant financial costs and risks to the patient. Furthermore, implanted VNS can induce bradycardia, hoarseness, cough, and nocturnal dyspnoea during stimulation which can limit tolerability and dose [4].

It is now possible to stimulate the vagus nerve transcutaneously [5] either at the external ear (auricular branch) or at the neck (cervical branch). Several devices are available to do this. For example the NEMOS® (Cerbomed, Germany) stimulates at the concha of the outer ear and is CE-(European Conformity) marked for the European market. There is also a hand-held stimulator Gammacore (Electrocore) which is a now Food and Drug Administration (FDA)-approved treatment for migraine and cluster headache and is applied at the neck. If safe and tolerated by patients, such non-invasive forms of stimulation may have similar therapeutic benefits compared to implantable VNS devices whilst avoiding the need for surgery. However, the range of side effects and adverse events from tVNS has not been systematically evaluated. To inform researchers, clinicians and patients using tVNS we therefore performed the first ever systematic review of studies reporting tVNS treatment-harms.

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2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria including the "extension" for systematic reviews of treatment harms were followed [6]. The Cochrane Adverse Effects Methods groups' framework was also used to guide the review process [7]. The review protocol is registered on PROSPERO International prospective register of systematic reviews (CRD42017065499).

We searched databases MEDLINE via Ovid, Scopus and Web of Science using the terms: (vagus nerve stimulation OR vagal nerve stimulation OR VNS) AND (transcutaneous OR transdermal OR transdermic OR nvns OR noninvasive OR non-invasive OR tVNS OR t-VNS OR cervical OR auricular OR external) AND English [Language]. The "grey" literature, was also searched via the US National Institutes of Health ClinicalTrials.gov website, EThOS (e-thesis online service), ProQuest and opengrey. eu. Electronic searches were limited to human subjects from the outset and any animal studies inadvertently identified were excluded during sifting. Studies involving auricular acupuncture were excluded, as a safety review of this technique was published recently [8].

Review articles were allowed in the initial search so that they could be scrutinised later by the authors in case they contained information regarding tolerability of tVNS. However, only original research studies were included in the final set of studies for data extraction. Finally, the main manufacturers of tVNS devices, Cerbomed GmbH (NEMOS®) and ElectroCore LLC (Gammacore) and Auri-Stim Medical Inc. (NET-1000/2000/3000) and Tinnitus treatment Centre (ParaSym previously known as Salustim), were consulted about side effects associated with their stimulators.

2.1. Identification of studies from bibliographic databases

Two authors (JR and DD) independently searched the literature in stages (titles, then abstracts, then full text searches) (Fig. 1). The last search was completed on 09/05/2017. Studies were selected if they had deployed tVNS in human subjects regardless of study type, size or disease/condition being studied. If either author considered a paper might be relevant, the paper was taken to the next stage of sifting. Any disagreements regarding inclusion of a paper at the end were resolved by consensus.

Any original studies in which safety or tolerability data were available were selected for data extraction. Where studies did not report on safety or tolerability, the corresponding author named on the paper was contacted by e-mail for any such data pertaining to the study. Where more than one article reported on the same dataset, the paper reporting the most recent version of the data was taken. Once the final set of papers for data extraction were known, their reference lists were hand-searched by two authors (JR and DD) for any additional potentially relevant publications. Finally, the contents pages of the 3 journals contributing the largest numbers of publications were searched dating back to the year of publication of the earliest study (2007).

2.2. Data extraction

We recorded study population, publication type, stimulation dose parameters (location, pulse width, frequency, intensity, duty cycle), side effects (nature of and number of participants experiencing) and their methods of measurement, adverse events (definition, description, prevalence, severity) and numbers of study drop-outs due to side effects/adverse events (AE) in the tVNS-treated participants.

An AE was deemed "Serious" if the authors of the relevant study had described it as such, regardless of whether SAE was defined formally in the methods. Since participants with a history of cardiac diseases are often excluded from studies involving tVNS, we also recorded the terminology used by authors to exclude such participants. Bradycardia was only considered to be a side effect if it had caused symptoms in the participant.

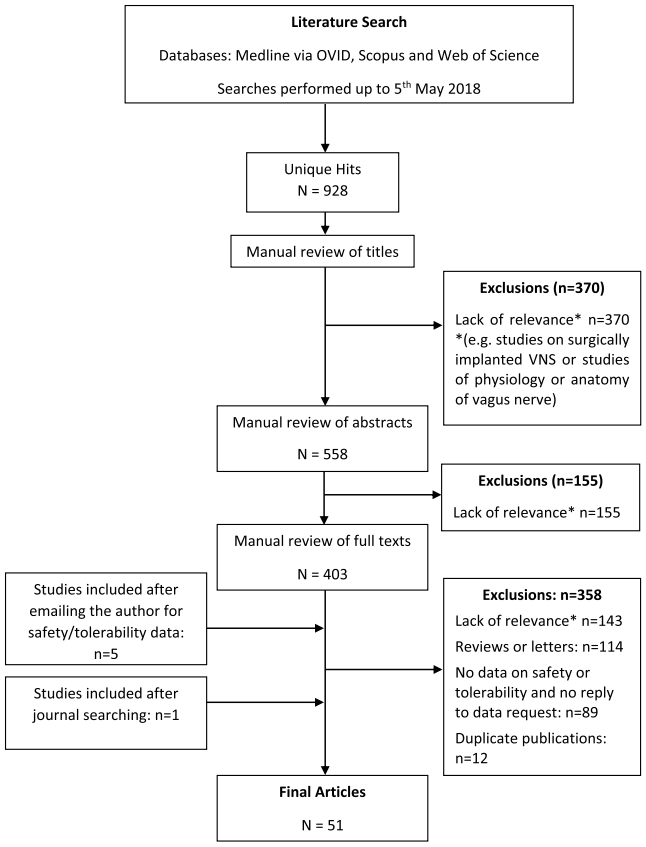

Fig. 1. Flow diagram showing numbers of publications excluded at each stage of sifting.

2.3. Statistical analysis

Side effects reported were grouped according to body system involved e.g. cardiovascular, ear nose and throat etc (Table 2). Descriptions of skin sensations e.g. pruritis, dysaesthesia, skin irritation were grouped together under the term "LOCAL" side effects (Table 2). The overall percentage of participants experiencing each side effect across the studies was then calculated, using the total number of subjects receiving tVNS across all studies as the denominator. For studies that reported the number of participants experiencing "any" side-effect (i.e. one or more side effects of any type) and where tVNS exposure-time per subject could be derived, an exposure-adjusted event rate was calculated. For example, if participants received tVNS 4 h per day for 6 months, the cumulative exposure time was calculated as $4 \times 60 \times 180 = 43200$ min, and this was multiplied by the number of participants and divided by 60 to determine the number of patient hours.

Where cumulative exposure was within a range, or in studies where participants were allowed to deliver additional doses as required, the minimum tVNS exposure-time was used in this calculation. The number of participants with side effects was then divided by the number of patient hours and multiplied by 100 (for graphical display purposes) to obtain the rate of side effects per 100 h of stimulation. This rate (with 95% confidence interval [9])

Table 1
Summary characteristics of 51 selected studies.

Author, year, reference	Population	Study type	N tVNS	Site of tVNS	Side of tVNS	Pulse width (ms)	Frequ-ency (Hz)	Intensity (mA)	Dose schedule	Cumulative exposure time (mins)	Cardiac Exclusion Criteria	n (%) participants with "any" side effects	Side effect rate per 100 h of tVNS[a]	N Drop-outs due to Side effects
Aihua 2014 [10]	Epilepsy	RCT	30	External auditory canal + conchal cavity	Both	NR	20	NR	20 min, 3 times/ day, 12 months	21900	Serious heart disease, pacemakers	4 (13)	0.04	1
Altavilla 2015 [11]	Chronic migraine	Experimental	20	Neck	NR	NR	NR	NR	One dose for 90 s	1.5	None stated	0	0	N/A
Assenza 2017 [12]	Epilepsy	Case report	1	External acoustic meatus	L	NR	NR	NR	4 h/day, 6 months	43200	None stated	1	–	0
Badran 2015 [13]	Healthy volunteers, safety/tolerability	Experimental	15	Tragus	L	0.1 of 0.2 or 0.5	1 or 10 or 25	1.5–4.64	60 s	1	None stated	0	0	N/A
Barbanti 2015 [14]	Migraine	Single arm trial	48	External acoustic meatus	R	NR	NR	NR	Per migraine: 2 × 120s doses, 3 min apart. Max of 3 migraines treated in 2 weeks	Unable to calculate	History of cardiovascular or atherosclerotic disease	32 (67)	–	0
Bauer 2016 [15]	Epilepsy	RCT	37	Concha	L	0.25	25	Tingling without pain	30s on/off. 4 hrs/ day. 20 weeks	16800	Relevant cardiac disease	NR	–	9
Burger 2016 [16]	Fear extinction in healthy volunteers	RCT	18	Concha	L	NR	25	0.5	30s on/off	Unable to calculate	Cardiac arrhythmia, cardiac disease	NR	–	0
Busch 2013 [17]	Pain perception in healthy volunteers	Experimental	48	Tragus	L	0.25	25	0.25–10 (mean 1.6 standard deviation 1.5)	20min single session	20	Any cardiac diseases	NR	–	0
Capone 2014 [18]	Cortical excitability in healthy volunteers	Experimental	10	Tragus	L	0.3	20	8	30s on/4.5 min off. 60 mins single session	6	None stated	0	0	0
Cha 2016 [19]	Benign positional vertigo	Case report	1	Concha (cymba and cavum) and tragus	R	0.2	30	Just below dis-comfort threshold	4 min each site	12	None stated	1	–	0
Clancy 2014[a] [56],	Autonomic function in healthy volunteers	Experimental	34	Tragus	Both	0.2	30	Sensory threshold (10 –50)	Continuous, 15 min single session	15	Previous cardiovascular disease or hypertension	0[a]	0	N/A
Davies 2016 [20]	Hemicrania continua	Case series	3	Neck	NR	NR	NR	NR	NR	Unable to calculate	None stated	0	–	0
Dietrich 2008 [21]	Experimental-fMRI changes	Experimental	4	Tragus	L	0.25	25	4–8	50s on/100s off. 4 times	3.3	None stated	0	0	0
Finetti 2015 [22]	Dravet syndrome	Case report	1	NR	NR	NR	NR	NR	NR	Unable to calculate	None stated	0	–	N/A
Frangos 2016[a],[b],[57]	Experimental-changes on fMRI	Experimental	13	Neck	R	1	25	0–48 V	Continuous 2 min	2	None stated	0*	0	N/A
Frokjaer 2016[a] [58],	Musculoskeletal pain thresholds and gut motility	Experimental-crossover	18	Concha	L	0.25	30	0.1–10	60 min stimulation	60	None stated	0*	0	N/A
Garcia 2016[a] [59],	Migraine	Experimental	16	Ear	NR	0.45	30	Moderate to strong (not painful)	Stimulated for 6 min during fMRI scan	6	None stated	0*	0	N/A

(*continued on next page*)

Table 1 (*continued*)

Author, year, reference	Population	Study type	N tVNS	Site of tVNS	Side of tVNS	Pulse width (ms)	Frequ-ency (Hz)	Intensity (mA)	Dose schedule	Cumulative exposure time (mins)	Cardiac Exclusion Criteria	n (%) participants with "any" side effects	Side effect rate per 100 h of tVNS[a]	N Drop-outs due to Side effects
Gaul 2015[b],[23]	Cluster headache (CH)	RCT	48	Neck	R	1	25	Up to 60 mA or 24 V	3 × 2 min stimulations. 5 mins apart. Twice daily for 8 weeks with optional extra doses for acute CH attacks	≥672	Known or suspected cardiac/ cardiovascular disease	25 (52)	4.65	7
Goadsby 2014[b],[24]	Migraine	Single arm trial	27	Neck	R	NR	NR	NR	2 × 90s doses, 15 min apart, for moderate/severe pain or after 20 min of mild pain (up to 4 attacks in 6 weeks	Unable to calculate	Clinically significant irregular heart rate or rhythm, pacemaker	13 (48)	–	0
Grazzi 2014 [25]	Migraine	Single arm trial	30	Neck	R	NR	NR	NR	1 × 90s dose, for 3 −6 migraine attacks	4.5	None stated	0	0	N/A
Grazzi 2016[b],[26]	Menstrual migraine	Single arm trial	51	Neck	Both	1	25	Up to 60 mA or 24 V	Bilateral 2 min stimulations, 3 times/day. 10−14 days/month for 3 months	180−252	None stated	NR	–	1
Grazzi 2016[b],[27]	Migraine without aura	Case series	8	Neck	R	NR	NR	NR	2 min stimulation repeated within 1 h if needed. 4−8 migraines within 1 month.	Unable to calculate	None stated	0	–	0
Hasan 2015[b],[28]	Schizophrenia	Crossover RCT	17	Outer ear canal	L	0.25	25	0.1−10	30s on/180s off. All day for 14 weeks (or 26 weeks if active arm). Lead in phase.	10080 or 18720	Implanted medical device	2 (12)	0.07	0
He 2013 [29]	Paediatric epilepsy	Single arm trial	14	Concha	Both	NR	20	0.4−1	3 × 30 min/day. 6 months	16200	Severe heart diseases	2 (14)	0.05	0
Hein 2013 [30]	Depression	RCT	18	Concha	Both	NR	1.5	Study 1: 0−0.6. Study 2: 0.13	15 min, once or twice daily. 5 days/ week. 2 weeks	150 or 300	Cardiac diseases	0	0	0
Huang 2014 [31]	Impaired glucose tolerance	RCT	36	Concha	NR	≤1	20	1	Twice daily, 20 min post-prandial. For 12 weeks.	3360	Risk of serious cardiovascular disease	2 (6)	0.1	2
Jacobs 2015 [32]	Associative memory performance	Crossover RCT	30	Tragus	L	0.2	8	5	2 times/day. 7−10 days off	Unable to calculate	Cardiac diseases	NR	–	0
Kinfe 2015 [33]	Cluster-tic syndrome	Case report	1	Neck	R	1	25	Up to 14 V	90s twice/day and at onset of every migraine attack for 24 days.	≥72	None stated	0	–	0
Kinfe 2015 [34]	Migraine, sleep disturbance depression	Single arm trial	20	Neck	Both	1	25	0−24 V	2 × 2 min stimulations, twice day for 3 months with optional additional acute treatments	≥720	Cardiovascular disease	4 (20)	1.67	0
Kraus 2007 [35]	Healthy volunteers, fMRI changes	Experimental	25	Tragus	L	0.02	8	4−5 mA or 30.7 −33.1 V	30s on 2 min off. Stimulated 3 times with tVNS on 2	6	None stated	0	0	0

									consecutive days (study then repeated with fMRI)					
Kreuzer 2014 [36]	Tinnitus	Single arm trial	Phase 1: 24, Phase 2:26	Concha	L	NR	25	0.1–10	Phase 1: 30s on/ 180s off ≥6 h per day for 6 months. Phase 2: 30s on/off 4 h/day for 6 months.	Phase 1 participants: 9257				
Phase 2 Participants: 21600	Pacemaker	NR	–	N/A										
Laqua 2014 [37]	Healthy volunteers, pain threshold	Crossover, experimental	22	Concha	Both	0.2	2 Hz and 100 Hz bursts	Maximal not painful	30 min single session	30	None stated	1 (5)	9.09	1
Lehtimaki 2013 [38]	Tinnitus	Single arm trial	10	Tragus	L	NR	25	Around 0.8 mA	7× (45–60 min) sessions. Over 10 days	367.5	None stated	0	0	0
Lerman 2016 [39]	Healthy volunteers nociceptive effects	Experimental RCT	10	Neck	Both	1	25	Up to 60 mA or 24 V	2 × 90s stimulations. 3 times in one day	9	Previous cardiovascular disease	NR	–	1
Magis 2013 [40]	Headaches	Single arm trial	18	Neck	NR	NR	NR	NR	90s 3 times per day	Unable to calculate	None stated	NR	–	6
Marin 2016† [41]	Cluster headache	Single arm trial	30	Neck	NR	NR	NR	NR	NR	Unable to calculate	None stated	0	–	N/A
Napadow 2012 [42]	Pelvic Pain	Crossover trial	18	Concha	L	0.45	30	Moderate to strong (not painful)	2 × 30min sessions. 1 week apart	60	Previous severe cardiac disease	0	0	0
Paulon 2015 [43]	Gastroparesis	Single arm trial	23	Neck	Both	NR	NR	NR	2 × 120s doses 8 hourly for 2 weeks and 3 doses 8 hourly for 1 more week	1176	None stated	0	0	0
Rong 2014 [44]	Epilepsy	Non-RCT	50	Concha	NR	≤1	20–30	1	30 min. Twice per day. 24 weeks	10080	Pulmonary heart diseases	NR	–	3
Rong 2016 [45]	Depression	Non-RCT	160	Concha	NR	0.2	20	Around 4 –6 mA	30 min, twice per day for either 8 or 12 weeks (if active arm)	3360 or 5040	None stated	2 (2)	0.02	0
Schulz-Stubner 2011 [46]	Hiccups	Case report	1	Neck	L	NR	1 Hz	6	30s on, then brief tetanic stimulus applied	0.5	None stated	1	–	0
Silberstein 2016[b],[47]	Migraine	RCT	30	Neck	R	NR	NR	Up to 60 mA or 24 V	2 × 2 min stimulations, 5 –10 min apart, 3 times/day for 6 months (or 8 months if active arm)	2160 or 2880	Known or suspected cardiovascular disease	NR	–	0
Silberstein 2016[b],[48],	Cluster headache	RCT	73	Neck	R	1	25	Up to 60 mA or 24 V	3 × 2 min stimulations at the onset of symptoms or pain. Up to 5 attacks (double blind phase) or unlimited use (open label phase)	Unable to calculate	Prolonged QT interval or arrhythmia, cardiovascular disease	6 (8)	–	1

(continued on next page)

Table 1 (*continued*)

Author, year, reference	Population	Study type	N tVNS	Site of tVNS	Side of tVNS	Pulse width (ms)	Frequ-ency (Hz)	Intensity (mA)	Dose schedule	Cumulative exposure time (mins)	Cardiac Exclusion Criteria	n (%) participants with "any" side effects	Side effect rate per 100 h of tVNS[a]	N Drop-outs due to Side effects
Stavrakis 2015 [49]	Induced Atrial Fibrillation	RCT, experimental	20	Tragus	R	1	20	Lowest voltage that slowed sinus or atrial-his rate	Continuous stimulation for 60 min following induction of AF	60	Left ventricular dysfunction, valvular disorder	2 (10)	10	N/A
Steenbergen 2015 [50]	Action cascading in healthy volunteers	RCT	15	Concha	L	0.2–0.3	25	0.25	30s on/off. 45 mins	22.5	Implanted medical device	0	0	0
Stefan 2012† [51]	Epilepsy	Single arm Trial	10	Tragus	L	0.3	10	Average of 25 V	3 × 1hr per day. 9 months	48600	"Same as invasive VNS exclusion criteria"	1 (10)	0.01	0
Steyn 2013[b],[52]	Asthma	Case series	4	Neck	NR	NR	NR	NR	2 × 60s stimulations, 30 min apart	2	None stated	0	0	0
Straube 2015 [53]	Migraine	RCT	23	Concha	L	0.25	25	NR	30s on/off. 4 h/day. 12 weeks. Additional hour if desired	10080	None stated	NR	–	3
Trevizol 2015 [54]	Depression	Case report	1	Mastoid process	NR	0.25	120	NR	10 daily sessions, 30 min s/day	300	None stated	0	–	0
Trevizol 2016 [55]	Depression	Single arm trial	12	Mastoid process	Both	0.25	120	12	10 sessions of 30 min over 2 weeks	300	None stated	12 (100)	20	0
Weise 2015[a] [60],	Parkinsons disease	Experimental	100	Tragus	Both	0.1	0.5	8	Until 100 artefact free epochs recorded	Unable to calculate	None stated	100 (100)[a]	–	0

[a] Data on side effects/adverse events provided by authors following request for data (5 studies).
[b] Industry-sponsored studies.

Table 2
Type of Side effects experienced by participants in included studies.

Side Effects	No. of studies	No. with side effect (% of participants across all studies given, where >1%)
LOCAL		
Tingling/pain/redness/itching	20[a]	240 (16.7)
Gastointestinal		
Nausea/vomiting	6 [15,32,36,46,47,55]	16 (1.1)
Diarrhoea	1 [15]	5
Strange feeling in stomach	1 [17]	1
Constipation	1 [51]	1
EAR, NOSE AND THROAT		
Dysphagia	1 [17]	1
Oropharyngeal pain	1 [23]	4
Voice alteration/hoarseness	3 [24,36,51]	4
Tinnitus	2 [24,45]	2
Deafness	1 [36]	1
Nasopharyngitis	2 [15,23]	23 (1.6)
Vertigo	1 [15]	7
CARDIOLOGICAL		
Palpitations	2 [15,40]	2
Arrhythmia	1 [36]	2
Hypotension	1 [37]	1
Bradycardia	1 [37,46]	1
Left Bundle Branch Block	1 [36]	1
NECK		
Neck pain	4 [23,32,36,39]	5
Neck stiffness	1 [24]	5
Neck twitching	3 [24,26,34]	6
Neck spasm	1 [40]	1
GENITO-URINARY		
Urinary frequency	1 [24]	4
Vaginitis	1 [47]	2
PAIN		
Shoulder pain	1 [24]	2
Joint pain	1 [24]	1
Back pain	1 [47]	2
Tooth pain	1 [47]	1
Chest pain	1 [36]	3
NEUROLOGICAL		
Headache	8 [15,23,32,36,39,47,51,55]	47 (3.3)
Paraesthesia/numbness	3 [12,36,47]	12
Facial drooping	2 [24,48]	19 (1.3)
Metallic taste	1 [48]	2
Tonic muscle contraction	1 [40]	3
Eye twitch	1 [47]	2
PSYCHIATRIC		
Depression	1 [23]	1
Concentration problems/Mood changes	1 [32]	1
INFECTIVE		
Flu-like symptoms	2 [24,47]	2
Upper respiratory tract symptoms	1 [47]	4
Fever	1 [24]	1
OTHER		
Dizziness/syncope	8 [10,15,23,24,31,32,36,44]	20 (1.4)
Drowsiness	2 [10,55]	13
Fatigue/tiredness	3 [15,32,40]	7
Shortness of breath	1 [36]	5

[a] 20 studies [14, 15, 36,39, 40, 44,47–49,53, 55, 60,17, 19, 24,26, 28, 29,32,34].

was shown for each study in a forest plot presented on a log scale, with zeros replaced with a value of 0.001 to allow display (Fig. 4).

To explore the influence of tVNS dosage on side effects, bubble plots (Fig. 5) were created to show exposure-adjusted side effect rates per 100 h of tVNS against pulse width (ms) and frequency (Hz). If studies stated that tVNS frequencies or pulse widths were within a specified range, these studies were excluded from the bubble plots as it could not be established which doses had been

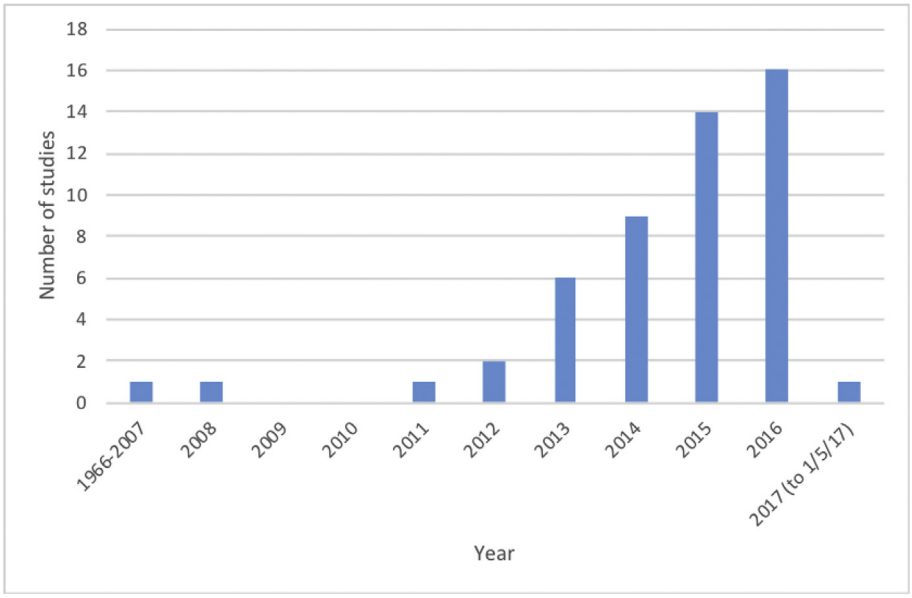

Fig. 2. Year of Publication of Papers providing tVNS safety/tolerability data.

delivered to the participants who had experienced the side effects. The size of the bubbles in these plots represent the size (n participants) of the studies (single-person case reports were excluded). P values for the effect of frequency and pulse width on side-effect rates were calculated using Poisson regression meta-analysis models.

3. Results

The initial search yielded 928 publications (Fig. 1). Following evaluation of study titles, 370 publications were excluded due to non-relevance to the research question. Examples of non-relevant papers included animal studies, those which involved surgically implanted VNS and physiology/anatomy studies of the vagus nerve/vagus nerve function. A further 513 studies were excluded following review of abstracts and full texts leaving 45 studies [9–18], [18-36], [36-54] which deployed tVNS in humans and where quantitative safety and/or tolerability data were reported. Authors of 5 studies sent us previously unpublished data regarding safety and/or tolerability of tVNS, allowing their inclusion in this review [56–60]. One further publication [25] was included after searching the contents pages of the 3 most common journals of publication. On further scrutiny, that paper had not used the term "vagus nerve stimulation" anywhere in the title or abstract, instead referring to the device name "Gammacore" throughout. Furthermore, when we re-ran the initial database searches incorporating the text word "Gammacore" and no further relevant studies were found. Thus, 51 studies were used for data extraction. Summary characteristics of these studies are provided in Table 1.

The included papers were published from 2007 to 2017 (Fig. 2) and comprised 35 full papers, 10 abstracts and 6 letters to the editor. In total, there were 28 Clinical trials, 14 experimental studies and 9 case reports/series (Table 1).

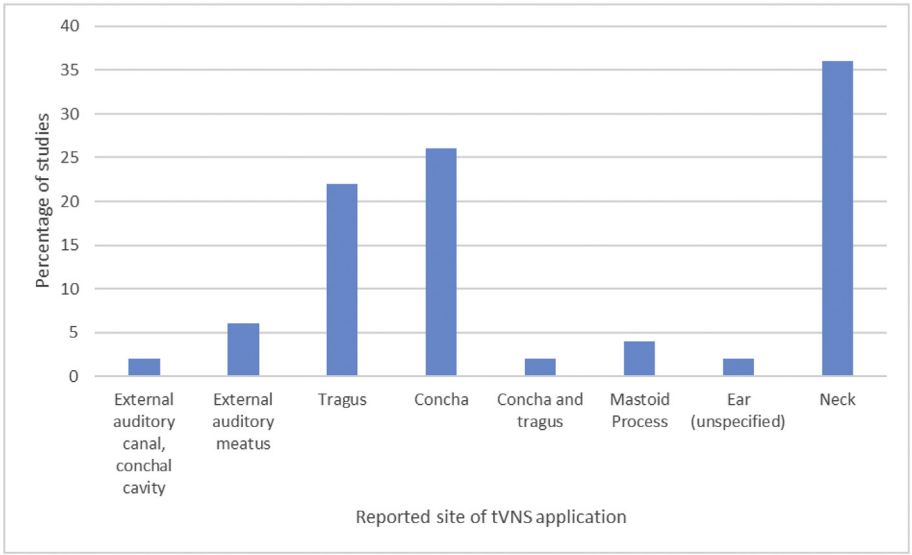

Fig. 3. Site of tVNS stimulation for participants in the included studies (NB. one single-person case study excluded as no site of stimulation given).

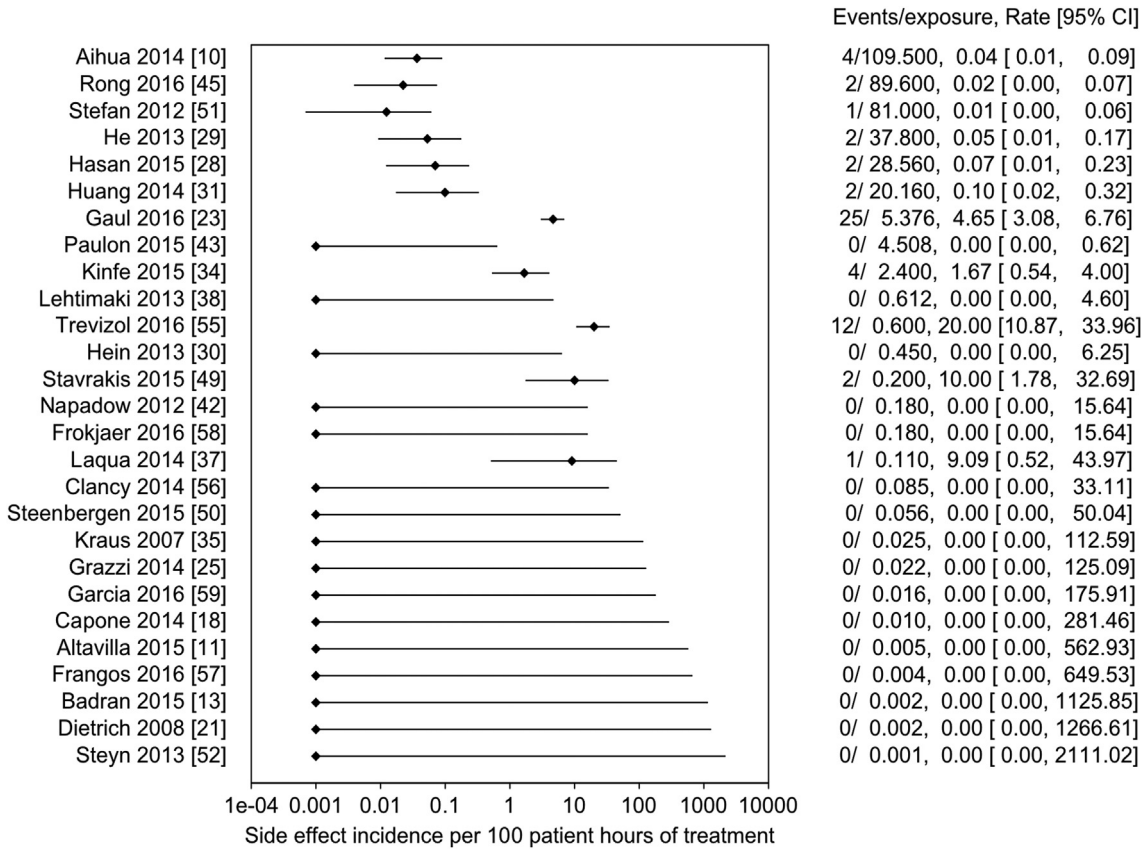

Fig. 4. Forrest Plot: Incidence of side effects per 100 h of tVNS where calculable (single study case reports were excluded).

The most frequent journals of publication were Brain Stimulation (n = 9), the Journal of Headache and Pain (n = 6) and Cephalgia (n = 5). Of the papers that disclosed funding sources, 11 publications noted financial support or involvement from one of the main device manufacturers (labelled with † in Table 1) e.g. ElectroCore LLC (9 studies) [23,24,26,27,41,47,48,52,57] and CerboMed (2 studies) [28] [51].

3.1. Study populations

In total, across all 51 studies, 1322 participants received tVNS. The majority of studies treated patients with epilepsy (5 studies), migraine or cluster headache (15 studies), tinnitus (2 studies) and depression (4 studies). Other studies deployed tVNS in patients with schizophrenia, impaired glucose tolerance, pain, refractory gastroparesis, atrial fibrillation and asthma. Several studies administered tVNS to healthy volunteers e.g. to determine physiological/autonomic effects of tVNS, its effects on cognitive processes or tVNS effects on brain signal changes on functional magnetic resonance imaging (Table 1). Twenty studies (39.2%) excluded patients with a history of cardiac diseases but the definition of "cardiac disease" was often vague or ambiguous (Table 1).

One study (abstract only) evaluated safety and tolerability and changes in heart rate in healthy volunteers exposed to different stimulation settings. In that study, all settings were tolerated but a pulse width of 0.5 ms at a frequency 25 Hz resulted in the largest reduction in heart rate [13]. Another study published a retrospective review of cardiac safety after two adverse events (left bundle branch block and palpitations) occurred in 2 patients treated for tinnitus [36,61]. The authors of the latter study concluded that the cardiac aberrations were not due to tVNS and the trial continued with a different cohort of participants and intensified cardiac monitoring [36,61].

3.2. Stimulation site and parameters

The anatomical placement of the tVNS device varied with the majority of studies stimulating at the concha (14 studies) or the tragus (11 studies) of the ear or the cervical region (18 studies) (Fig. 3). Other sites of stimulation included the external auditory meatus and the Ramsay Hunt Zone (external auditory canal and conchal cavity). The tVNS was delivered on the left-side in 18 studies, the right-side in 11 studies, bilaterally in 12 studies and unknown side in 10 studies (Table 1).

Stimulation parameters varied widely but the most common frequencies were 25 or 20 Hz (range 0.5–120 Hz) with pulse widths usually 1 or 0.25 m s (range 0.02–1) (Table 1).

Stimulation intensity (amplitude (mA) or voltage) was often varied by participants themselves within studies or was pre-set according to participants' sensory or toleration threshold. Most studies, however, did not report the actual amplitudes used by the participants during the study (Table 1).

The dose "schedule" was commonly 30 s on/30 s s off for the duration that the stimulator was applied but this parameter was often not specified (Table 1). Most publications did not provide a rationale for the stimulation settings chosen but in one case report, the tVNS intensity was capped at 12–14 V because an animal study had demonstrated adverse events above this level [33].

Cumulative exposure time to tVNS for individual study participants could be calculated for 40 studies (Table 1) and ranged from 30 s [46] to 48600 min (3 h per day for 9 months) [51].

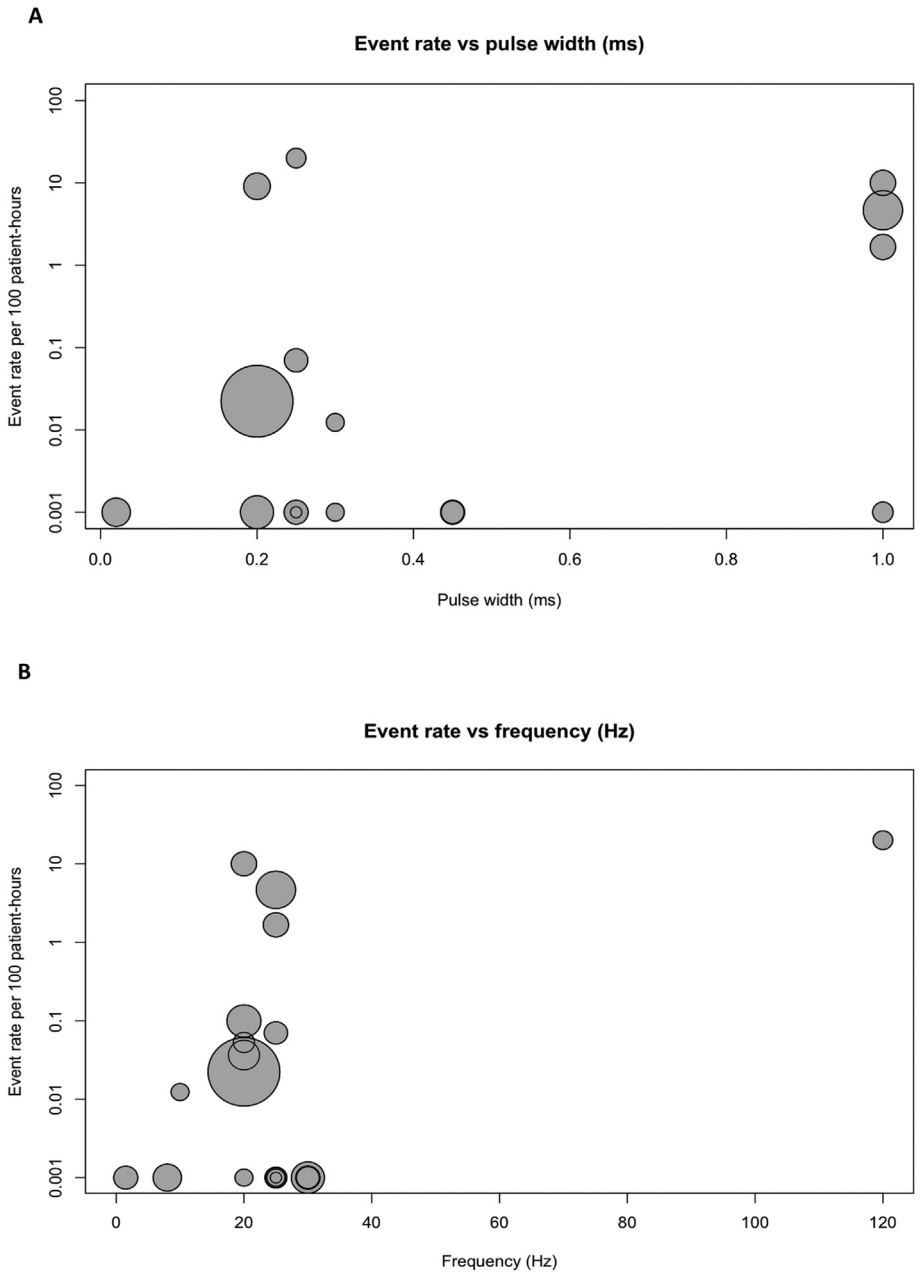

Fig. 5. Bubble Plots: Incidence of side effects (per 100 h of stimulation) according to a) pulse width (ms), b) frequency (Hz) of tVNS.

3.3. Measurement of side effects

Most studies did not report the methods they used to measure side effects or adverse events. However, a few studies gave participants a list of potential side effects and asked them to rate on 4 or 5 grade Likert scales the severity of each one [16,24,32]. Such side effect descriptions included “headache”, “neck pain”, “tiredness”, “nausea”, “skin irritation”, “concentration change”, “mood alteration”, “general discomfort” and “muscle contraction” [16,24,32]. One study, in participants with schizophrenia used the UKU (Udvalg for Kliniske Undersogelser) Side Effects Rating Scale which was originally designed for the registration of unwanted effects of psychotropic medications [28]. Other studies asked participants open-ended questions about side effects (with or without severity indicators) [18] [26], or asked them to document side effects in a diary [23,31] or questionnaire [51].

3.4. Type, severity and incidence of side effects

In 40 studies the number of participants with “any side effects” was reported (Table 1). Within this subset of studies, participants with side effects ranged from 0-100% and even after adjusting for cumulative exposure to tVNS, the side effect rate was highly variable between individual studies (P het <0.0001) (Fig. 4). Whilst the severity of side effects was infrequently reported, only 35 of the 1322 total participants (2.6%) dropped out of the various studies due to side effects and these were from within 10 (19.6%) studies [10,15,26,31,37,39,40,44,48,53]) (Table 1).

The most commonly reported side effect was skin irritation with 240 participants from 20 studies describing paraesthesia, tickling/prickling, erythema/redness, pruritus, dysesthesia, mild burns, discomfort/irritation, pressure, numbness, skin irritation or pain (Table 2). The two studies reporting 100% side effect rates had

disclosed "mild tingling under the electrodes" in all participants.[50,60} Other side effects reported amongst the various studies included; headache (47 participants from 8 studies), dizziness (20 participants from 8 studies), facial droop (19 participants from 2 studies), nausea (16 participants from 6 studies) and nasopharyngitis (23 participants from 2 studies). Pain distant to the stimulation site was felt by 9 participants e.g. at the neck (following ear stimulation), oropharynx, shoulder, chest, back, and teeth (Table 2).

A total of 5 studies (7 participants in total) reported cardiac side effects, including palpitations, arrhythmia, hypotension and bradycardia. Steyn et al. found that in 4 participants with asthma, the mean heart rate decreased from 106 to 85bpm 90 min following tVNS [52]. This heart rate reduction was asymptomatic, however in all cases. Similarly, in a case report by Schulz-Stubner and Kehl [46] there was a decrease in heart rate from 95 to 46bpm, in a patient receiving both tVNS and phrenic stimulation for hiccups on an intensive care unit. Symptomatic bradycardia occurred in one case-a healthy male volunteer who collapsed with bradycardia and hypotension during bilateral conchal tVNS (2–100 Hz, pulse width 0.2 m s) whilst also being subjected to a painful stimulus [37].

In the retrospective assessment of cardiac safety of tVNS by Kreuzer et al., two patients treated for tinnitus experienced cardiac arrhythmias (left bundle branch block and sinus arrhythmia) [61]. On thorough review of each case, the relevant researchers felt that both events were incidental to tVNS. However, tVNS tended to reduce the QRS complex duration on sequential ECGs and the authors recommend that future studies of tVNS in humans should include ECG monitoring as standard [61].

Gastrointestinal (GI) side effects were reported in 8 studies (Table 2). These included nausea and vomiting (16 participants, 1.2% total), diarrhoea (5 participants, 0.4% total). Nausea and/or dyspepsia were also described by two of the device manufacturers we contacted (Cerbomed, Electrocore) as occurring in "over 1%" of participants although exact numbers were not provided.

Miscellaneous other side effects were described in the published studies but these were rare e.g. constipation, depression, fever (Table 2).

3.5. Relationship between side effects and dose of tVNS

Due to absent reporting of certain parameters, only 20 studies could be included in the analysis of side effect rate vs. tVNS frequency (Hz) and 16 studies for the analysis of side effect rate vs. pulse width (Fig. 5). There was no significant relationship between pulse width and rate of side effects ($p = 0.09$) (Fig. 5). Whilst there was a significant relationship ($p = 0.008$) between side effect rate and tVNS frequency (Hz), this was largely due to the influence of one study that used a four-fold higher frequency than any other study and reported "100%" participants experienced side effects [55]. A sensitivity analysis excluding that study found no evidence of any association between side effect rate and tVNS frequency (Hz) ($p = 0.13$). Furthermore, due to under-reporting of dose parameters, a multiple regression analysis to determine independent effects on side effect rates was not possible.

3.6. Serious adverse events

Two studies gave a definition for "serious adverse event" [28,47] whilst the remainder did not formally define "serious". Overall, 30 SAE were reported, occurring in 22 participants from 7 studies [15,23,28,36,47,48,53]. Almost all SAE, however, were felt by the authors of the various studies to be unrelated to the tVNS. These included: 1× severe dizziness [10] 1 case of SUDEP (sudden unexpected death in epilepsy) [15], 1 cholecystitis [23], 1 haematoma [23], 2 appendectomies [28], 1 elective bowel operation [61], 1 fireworks exposure [36], 3 cardiac events [36] [15], 1 appendicitis [47], 1 worsening headache [47], 2 cluster headaches [48] (including 1 with a deep vein thromboses), 1 mesenteric ischaemia [48], 1 ureteral calculus [48], 1 infectious mononucleosis [53], 1 gastrectomy [53] and 2 intervertebral disc protrusion/herniation [53]. One subject suffered 5 SAEs including abdominal aortic aneurysm, pneumonia, anasarca, acute respiratory failure and urethral trauma [48].

Three SAEs were considered possibly or probably tVNS-related, and all occurred in the same study [15]. These included a case of palpitations (presumed due to vagally mediated parasympathetic innervation of the heart), a case of vestibular neuronitis (unclear why the authors felt this could be related to tVNS) and a skin lesion initially suspected to be a basal cell carcinoma (a diagnosis subsequently refuted on histology) [15]. In the latter case it was not stated by the authors whether the skin lesion had occurred at the site of the tVNS electrode placement.

4. Discussion

Whilst there have been reviews of treatment harms for older neuro-modulatory techniques such as transient direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), this is the first such review for tVNS. This review is needed since the rate of publications in which tVNS has been delivered to humans has been rising steadily for over a decade and there is growing interest in this technique amongst the research community. Furthermore, since tVNS recently received FDA approval for the treatment of migraine and cluster headache in 2017, sales of tVNS devices are likely to rise. Since clinical decisions need to account for risks to patients from tVNS as well as potential therapeutic benefits, this systematic review of tVNS safety and tolerability is important and timely.

We found that tVNS has been tolerated extremely well in research settings to treat a variety of neurological, and psychiatric disorders and has also been used safely in healthy volunteers e.g. to monitor its effects on autonomic function, functional brain imaging appearances and cognitive performance. Out of 1322 human subjects pooled from 51 studies, 3 serious adverse events were considered to be possibly due to tVNS and these were all from within the same study [15]. Furthermore, although a wide range of different side effects have been reported, these were either infrequent or tolerable, as very few participants dropped out of the studies due to side effects.

The low rate of cardiac arrhythmias is noteworthy as this is a recognised early and late complication of surgically implanted VNS [4]. Indeed, for invasive VNS, the FDA approves left sided vagus stimulation only as the left vagus carries fewer efferent nerve fibres to the heart than the right vagus. In this review, whilst most studies stimulated on the left side, some stimulated on the right or on both sides simultaneously. It was therefore reassuring that of 1322 treated, only 1 developed symptomatic bradycardia [37]. Furthermore, whilst 20/51 studies excluded patients with a history of cardiac diseases, the majority did not. Whilst we cannot infer from this that tVNS is safe in patients with a history of cardiac disorders (as we did not know the past cardiac histories of all the included participants), it is nonetheless reassuring that cardiac side effects were rare, particular as VNS is now being studied as a possible treatment for heart failure [3] and atrial fibrillation [49].

Only one study was specifically designed as a safety/tolerability study for tVNS. That study (published in abstract form) tested a range of stimulation parameters (0.1–0.5 m s pulse width, 1–25 Hz frequency. 0.99–4.64 mA intensity) in healthy volunteers to establish effects on tolerability and heart rate reduction [13]. The

study found that a stimulation pulse width of 0.5 ms at 25 Hz resulted in the largest reduction in heart rate compared to sham, and all doses were tolerated with no safety concerns. However that study was small (N = 15) and only one stimulus was given at each set of dose parameters [13] which limits generalisability of the findings to larger populations. Thus our finding that across all 51 identified studies (1322 humans treated with tVNS), only 35 participants dropped out due to side effects/AE will be reassuring to researchers, clinicians and future patients using tVNS.

In this study, we could not demonstrate a clear association between rates of side effects and tVNS stimulation doses. It is possible that as more data accrues, clearer trends might emerge. However, for such analyses to be performed, future studies will need to have reported the prevalence of side effects in a more consistent manner. For example, for consistency it would be helpful if all studies report the percentage of participants experiencing "any" side effects as well as the number of participants experiencing each side effect. In addition, the complete set of stimulation parameters, (pulse width, frequency, cumulative exposure, and amplitude (if known)) will be needed in order to show any independent effect of one stimulation parameter on safety and tolerability of tVNS.

4.1. Limitations

The major limitation is that a large number of studies deploying tVNS in humans had to be excluded from this review because they did not report any analysable data on safety/tolerability. Whilst this reflected the fact that none were designed "primarily" as safety studies, there may also have been some publication/reporting bias [40] potentially leading us to underestimate adverse events from tVNS. Whilst this was largely unavoidable, we went to lengths to minimise this risk. First, we searched the "grey" (unpublished) literature and reviewed abstracts as well as fully published peer-reviewed articles. Second, we asked a "broad sweep" research question (i.e. what side effects/adverse events might a patient experience when starting tVNS?) rather than focussing on a specific side effect/adverse event in detail. This latter method had the advantage of exposing previously unrecognised side effects from tVNS [7]. Third, by including all study types including case reports, editorial letters and experimental studies we further maximised opportunities to capture all possible evidence for treatment harms. Finally, we contacted the corresponding authors for missing data on safety/tolerability (Table 1). Nevertheless, there remains a possibility that side effects or adverse events have occurred from tVNS that are not amongst those in Table 1. Doctors and patients therefore continue to report adverse events from tVNS to the appropriate regulatory bodies.

There could also have been a bias toward under-reporting of side effects/SAE amongst studies which were sponsored by tVNS device manufacturers. Whilst any such bias cannot be easily quantified, it is noteworthy that several side effects and adverse events were reported from within those studies (asterisked in Table 1). Furthermore, the majority (40 studies, 1024 participants) were not commercially funded so it is unlikely that any such bias affected our findings significantly.

As has been noted by authors of other reviews of treatment harms [7], the methods used to determine side effects were variable and often not reported. Since "active" searching can overestimate adverse events, and "passive" reporting methods can underestimate them, it would be useful in the future if a consistent and validated approaches were used. The PRISMA guidance also encourages use of a standard definition for SAE [7] yet only 2 studies had done this [28,47]. We therefore encourage researchers collecting and reporting data on treatment harms to follow PRISMA guidance wherever possible to facilitate future reviews of this type.

A further limitation was that due to variability in the reporting of tVNS stimulation parameters and side effect rates, we could not use regression analysis to determine the sources of heterogeneity in side effect rates between studies. Nevertheless, this does not detract from the finding of low rates of study attrition due to side effects and lack of tVNS-attributable SAE amongst 1322 participants treated. These findings will assist with research study sample size calculations and consenting of participants as well as providing reassurance to doctors and patients using tVNS for clinical purposes.

Finally, as the FDA have recently approved tVNS for treatment of migraine, home-use of tVNS devices is likely to increase. It is possible that "real world" use of tVNS will give a different user-experience of tVNS. Doctors and patients should therefore continue to be encouraged to report adverse events to the regulatory bodies and this knowledge should be made publically available.

5. Conclusions

The available evidence to date suggests that tVNS is well tolerated in humans at the doses tested and is safe. The most common side effect is skin irritation at the stimulation site. Other side effects occurring in >1% of include; nasopharyngitis, headache, dizziness, nausea/vomiting, facial drooping. Serious adverse events were rare and none were confirmed to be due to tVNS. The following recommendations are made for tVNS researchers to facilitate future reviews on tVNS harms and any subsequent analysis of factors influencing the rates of side effects:

1. Report safety and tolerability data as routine in any study of tVNS in human subjects
2. Use a standard definition of SAE and a standardised method for measurement of side effects (e.g. open-ended questions about side effects with a severity indicator)
3. Fully disclose ALL tVNS stimulation parameters, including frequency, pulse width, amplitude and either the cumulative exposure time or the variables needed to calculate it.
4. Report the proportion experiencing "any" side effects as well as the proportion of participants experiencing each individual side effect.

Declarations of interest

None.

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